

Longitudinal study of vitals and laboratory measurements by patient's severity of COVID-19

Introduction

The severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) first emerged in Wuhan, China that has caused coronavirus disease in late 2019 (COVID-19) and started a pandemic with millions of fatalities.¹ The COVID-19 patients show diverse symptoms and disease trajectories that ranges from mild flu-like to severe respiratory complications and death. A variety of factors like demographics, comorbidities, ethnicity, and clinical parameters are associated with severity of disease and fatality.² In this study we are showing the trend in laboratory and vital measurements of inpatients admitted with mild, moderate or severe COVID-19 to understand if they differ among these groups at the beginning of hospital visit and how it changes with the progress of the hospital encounter. These clinical markers will help to stratify patients by the severity of COVID-19 during the course of hospitalization. Also, the longitudinal profiling of clinical and laboratory parameters is essential for clinical management by reducing clinical burden and lethal outcomes in critically ill patients. This study is similar to multi-dimensional studies on longitudinal data focusing on trajectory profiling, elucidating essential time-dependent relationship between clinical values, biomarkers and disease severity.³ The significant predictors can then be integrated into a machine learning model to predict the severity of COVID-19 and outcomes like mortality.^{4,5,6}

Method

This retrospective study was conducted on a sample taken from a mock-data derived from the National COVID Cohort Collaborative (N3C), a centralized, harmonized, high-granularity electronic health record repository of U.S. cohort of COVID-19 cases and controls.⁴ The study was conducted with randomly sampled 1763 patients who were classified as mild, moderate and severe COVID-19. Patients categorized as severe COVID-19 had a U07.1 diagnosis code or a positive lab test, and had a hospital visit between 7 days prior to and 14 days after a COVID diagnosis date, and had a procedure record for ECMO OR ventilator OR a medication record for a vasopressor during that hospitalization. Those labeled as moderate COVID-19 had all criteria of the severe except the procedure record for ECMO or ventilator OR a medication record for vasopressor during the hospitalization. And the rest of the patients were classified as mild. Only most popular measurement types were selected, these are the measurement types that appeared in the mock-data more than 214,000 times. There are 7,430 vitals and laboratory test records from the mild category, 139,518 records for the moderate and 72,974 records for the severe COVID-19 category. The data included 7 types of vitals and 15 types of laboratory tests. The 7 types of vitals are body temperature, diastolic blood pressure, heart rate, body weight, systolic blood pressure, oxygen saturation in arterial blood, and respiratory rate. And, the 15 types of laboratory tests are Erythrocytes [# /volume] in Blood by Automated count, Hemoglobin [Mass/volume] in Blood, Hematocrit [Volume Fraction] of Blood by Automated count, MCHC [Mass/volume] by Automated count, Glomerular filtration rate/1.73 sq M.predicted [Volume Rate/Area] in Serum, Plasma or Blood by Creatinine-based formula (MDRD), Protein [Mass/volume] in Serum or Plasma, Alkaline phosphatase [Enzymatic activity/volume] in Serum or Plasma, Alanine aminotransferase [Enzymatic activity/volume] in Serum or Plasma, Aspartate aminotransferase [Enzymatic activity/volume] in Serum or Plasma, Leukocytes [# /volume] in Blood by Automated count, MCV [Entitic volume] by Automated count, MCH [Entitic mass] by Automated count, Platelets [# /volume] in Blood by Automated count, Albumin [Mass/volume] in Serum or Plasma, and Bilirubin.total

[Mass/volume] in Serum or Plasma. The clinical parameters were visualized as a function of days from the date of diagnosis. The measurement's values were stratified by the severity group and the means with 95% confidence intervals were plotted by the day of the hospital visit for all the laboratory tests and vitals.

Results

In the cohort of 1,763 patients, 1,003 had mild, 541 had moderate and 219 had severe COVID. Table 1 summarizes the demographics of the mild, moderate and severe COVID-19 patients. The severe COVID group was older than the moderate and mild group, with more males than females. Among severe COVID patients 64% were >64 years of age. In moderate category 38% were between 46 and 65 years of age, and in mild category 40% were 18 to 45 years of age. Race distribution was similar between the groups with majority being white with 82% to 87% of the group's patient count.

Table 1 Summarized demographic (sex, age, and race) information for all 1763 patients in the sample categorized as Mild COVID, Moderate COVID and Severe COVID. No matching concept implies unknown race.

		Mild COVID n=1,003	Moderate COVID n=541	Severe COVID n=219
sex	female	518(52%)	299(55%)	92(42%)
	male	485(48%)	242(45%)	127(58%)
age	<18	186(19%)	35(6%)	2(1%)
	18-45	403(40%)	159(29%)	14(6%)
	46-65	234(23%)	204(38%)	62(28%)
	>65	180(18%)	143(26%)	141(64%)
race	asian	57(6%)	40(7%)	17(8%)
	black or african american	113(11%)	38(7%)	12(5%)
	no matching concept	7(1%)	6(1%)	NaN
	white	826(82%)	457(84%)	190(87%)

The number of vitals and laboratory measurements for the 14 days from the start of a hospital visit is disproportionately high for the moderate and severe categories, shown in Figure 1 for the seven vitals, and in Figure 2 for the 15 laboratory measurements. Even though there were more mild patients in the sample (1,003 mild patients, 541 moderate, and 219 severe patients), there were very few laboratory results and vitals data present for mild COVID-19 patients. Only 3.4% of the records are for the mild category. Of the 219,922 total measurements, 7,430 were for the mild patients, 139,518 were for the moderate, and 72,974 were for the severe categories. Also, the type of measurements taken for the mild patients were predominantly vitals and at the day of the hospitalization as shown in Figure 1. For instance, the oxygen saturation data was only measured at the time of hospitalization for mild patients, and only one measurement for body temperature was present on the 2nd and 11th day of hospital visit. Also, 7,319 of the mild category measurements belonged to the vitals and only 111 were present in the laboratory tests.

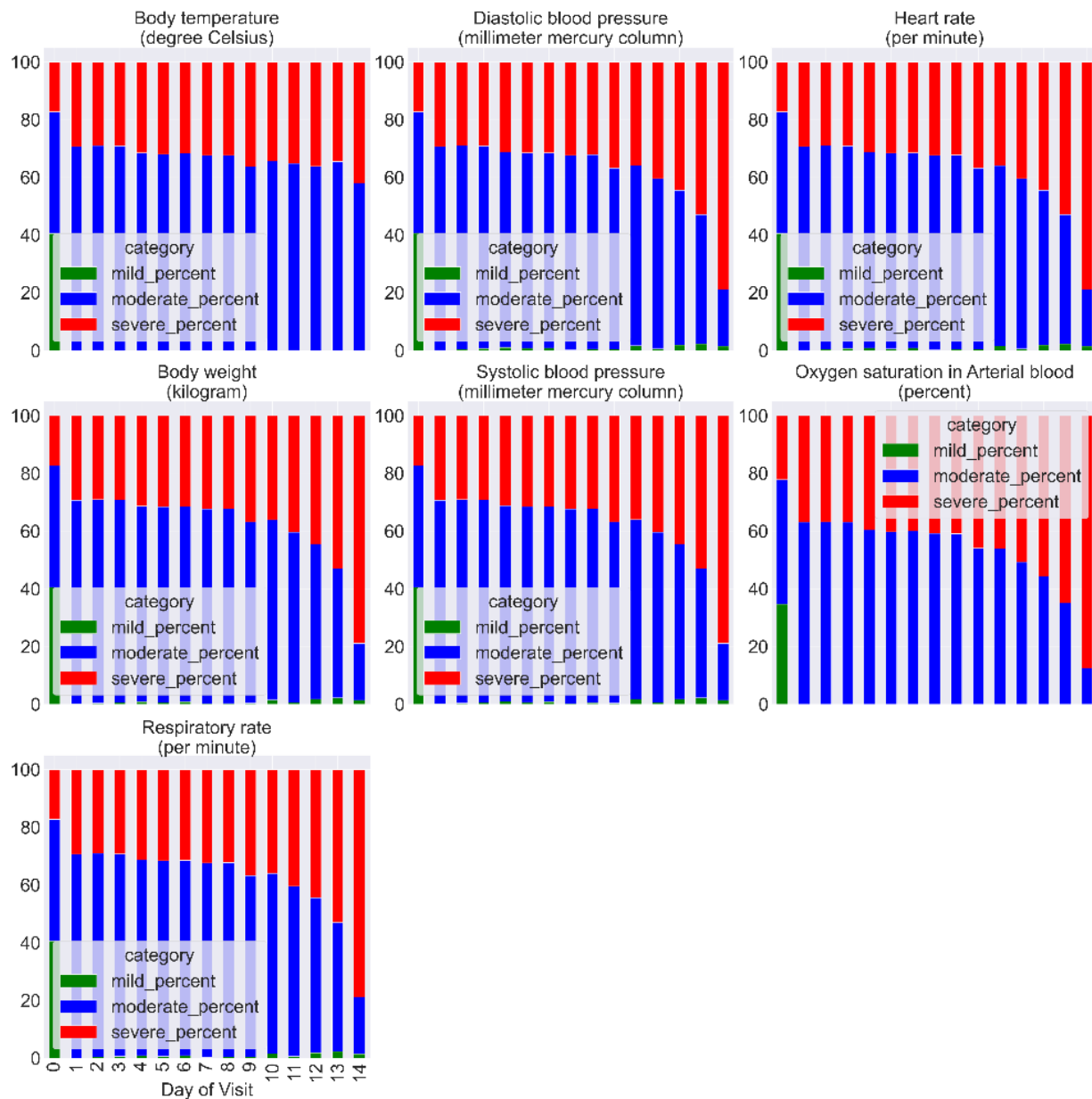


Figure 1 The composition of mild, moderate and severe measurements by the days from the hospital visit for the 7 vitals: Body temperature, Diastolic blood pressure, Heart rate, Body weight, Systolic blood pressure, Oxygen saturation in arterial blood and Respiratory rate. The units of measurements are shown in parenthesis in the titles. The mild is represented in green, moderate in blue and severe in red.

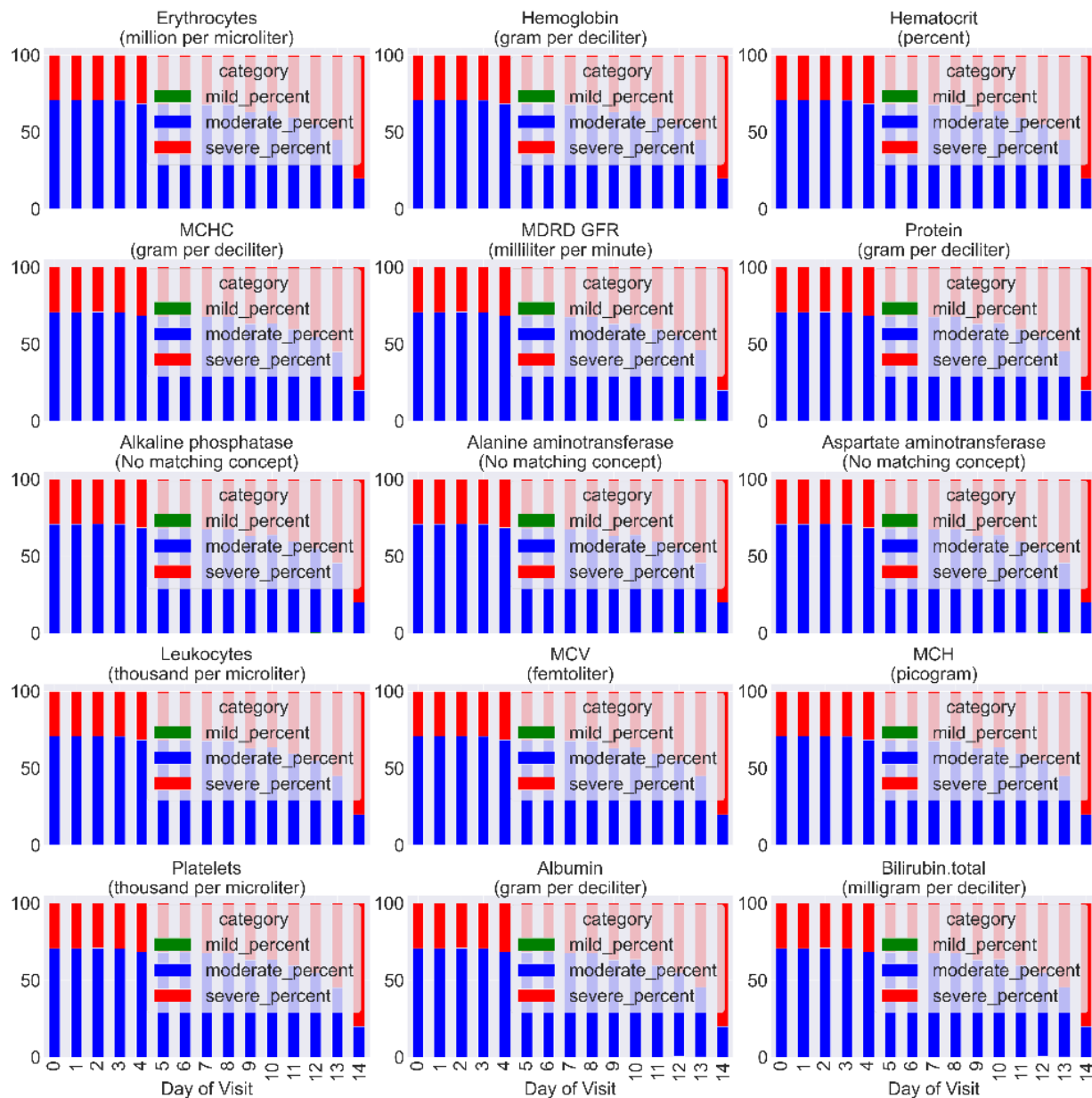


Figure 2 The composition of mild, moderate and severe measurements by the days from the hospital visit for the 15 laboratory measurements: Erythrocytes [# /volume] in Blood by Automated count, Hemoglobin [Mass/volume] in Blood, Hematocrit [Volume Fraction] of Blood by Automated count, MCHC [Mass/volume] by Automated count, Glomerular filtration rate/1.73 sq M.predicted [Volume Rate/Area] in Serum, Plasma or Blood by Creatinine-based formula (MDRD), Protein [Mass/volume] in Serum or Plasma, Alkaline phosphatase [Enzymatic activity/volume] in Serum or Plasma, Alanine aminotransferase [Enzymatic activity/volume] in Serum or Plasma, Aspartate aminotransferase [Enzymatic activity/volume] in Serum or Plasma, Leukocytes [# /volume] in Blood by Automated count, MCV [Entitic volume] by Automated count, MCH [Entitic mass] by Automated count, Platelets [# /volume] in Blood by Automated count, Albumin [Mass/volume] in Serum or Plasma, and Bilirubin.total [Mass/volume] in Serum or Plasma. The units of measurements are shown in parenthesis in the titles. The mild is represented in green, moderate in blue and severe in red.

Figure 3 and Figure 4 show the longitudinal trends of the vital and laboratory measurements respectively for the 14 days since the start of a hospital visit. Figure S1 and Figure S2 in the supplementary are provided for an enlarged view of the trendlines for moderate and severe categories. The infrequent records for the mild category during the hospital stay resulted in temporal fluctuations in the trend line for the mild category and missing confidence interval or wider confidence interval, if present.

As a hospital encounter progressed the severe and moderate patients continued to have more abnormal vitals compared to those with mild and moderate COVID. Only for some vitals after 10th day the values start improving for those with moderate COVID. An abnormal (higher) mean heart rate and respiratory rate were seen for the severe and moderate patients compared to those with mild COVID (see Figure 3). For some vitals like the mean body temperature and systolic blood pressure, as a hospital encounter progressed the severe COVID patients tended to have progressively more abnormal (higher) values than those with moderate and mild COVID (Figure 3 and Figure S1). Oxygen saturation continued to have more abnormal (lower) values for severe patients compared to moderate COVID patients, and cannot be compared to the mild patients due to lack of measurements during the course of hospitalization. For those with moderate COVID the mean body temperature starts decreasing from the 7th day of hospital visit, the mean systolic blood pressure progressively decreases from the 5th day, and the mean oxygen pressure spikes on the 13th day.

The laboratory measurements for the severe and moderate COVID patients continued to be progressively abnormal compared to the mild patients for 14 days from the start of the hospital stay. The mean values for hemoglobin, hematocrit, MCHC, MDRD GFR, protein, alanine aminotransferase, leukocytes, and platelets continued to be low, whereas mean values of albumin and bilirubin remained high compared to the mild COVID case. Only for the MCHC and MDRD GFR, mean values diverged for the moderate and severe patients after 10th day of visit, see Figure 4 and Figure S2. This indicates that a larger set of clinical parameters can be useful in differentiating the mild cases from the moderate and severe COVID-19 cases, however only a few types of measurements and their values after 10th day could be useful for setting apart the severe cases from the those with moderate COVID.

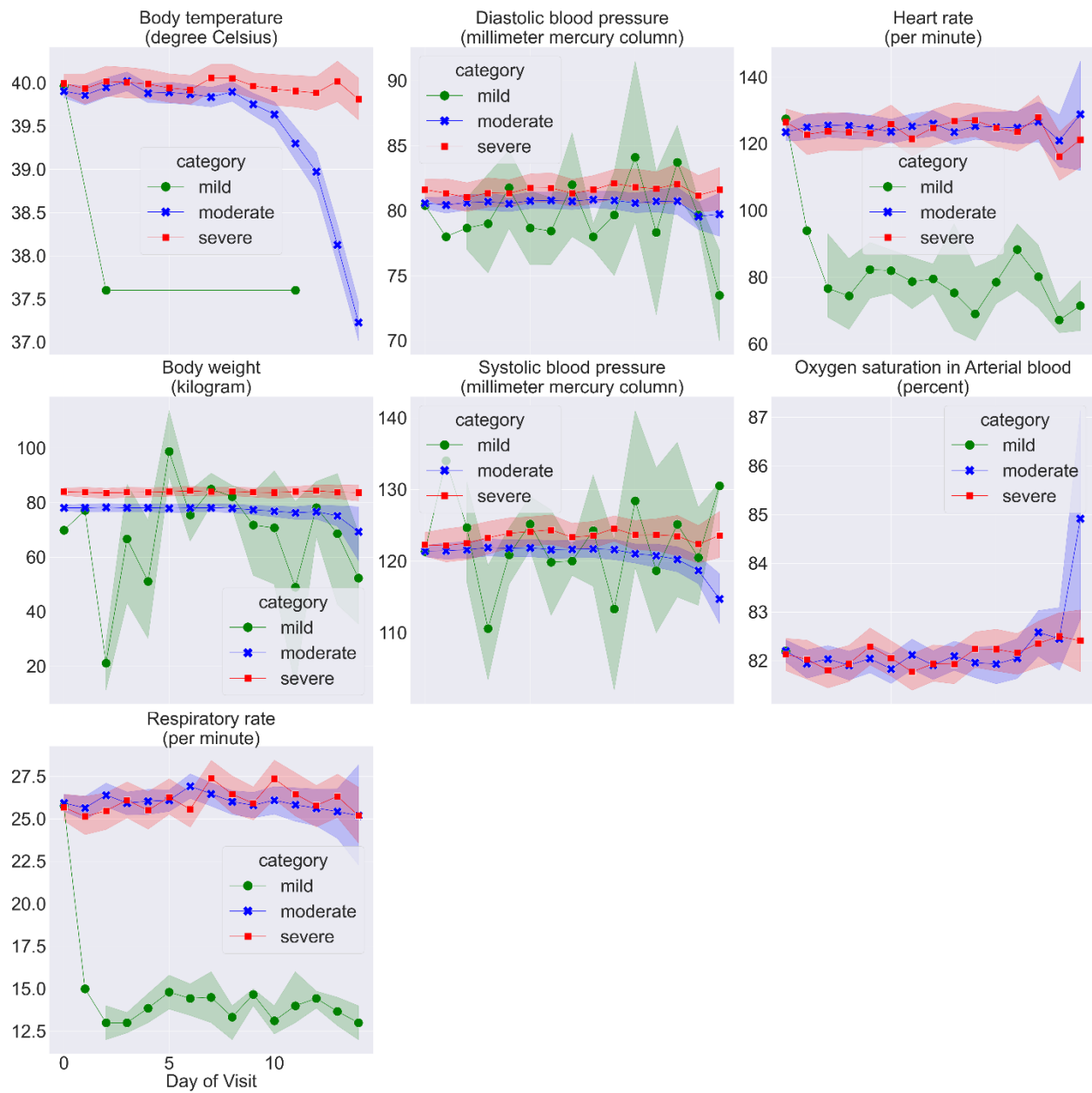


Figure 3 The mean (line) and interquartile range (shaded region) of each vital sign on each hospital day, stratified by patient severity of COVID-19 (mild [green], moderate [blue], and severe [red]).

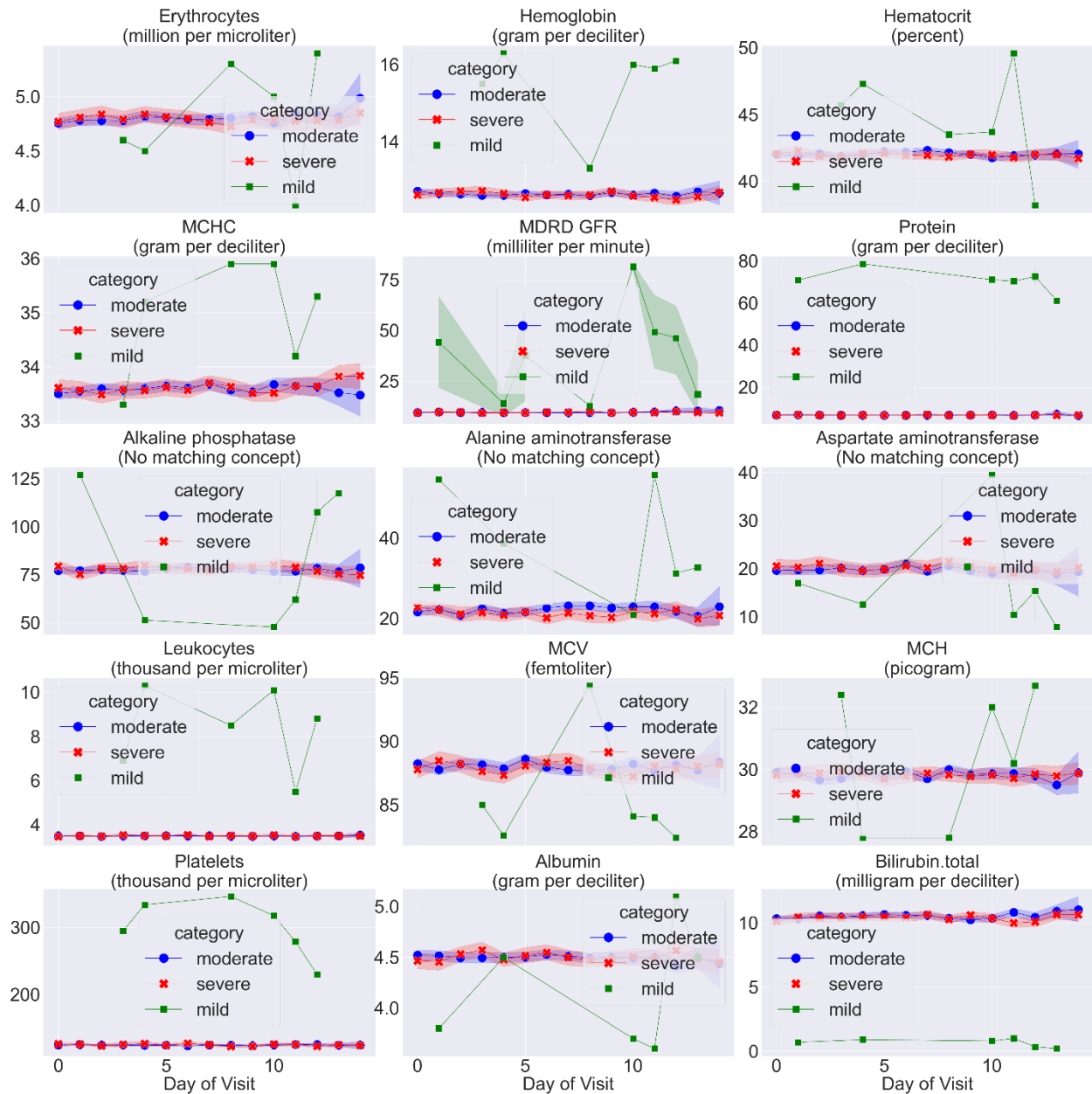


Figure 4 The mean (line) and interquartile range (shaded region) of each type of laboratory measurements on each hospital day, stratified by patient severity of COVID-19 (mild [green], moderate [blue], and severe [red]).

Discussion

The scarcity of measurements for the mild category provides challenges in the analysis of the mean values by the severity category as the hospital stay progressed. Also, most of these measurements belonged to vitals since only 111 out of 7,430 measurements were present for laboratory tests. As a result, significant temporal fluctuations were observed in the vitals and more in the laboratory measurements for the mild COVID-19 patients. In spite of such variation, it was clear that vitals and laboratory measurements progressed towards normal value within 1 to 2 days of hospitalization. These findings revealed that laboratory and vital information available early in the hospital course can help in differentiating mild

patients from the moderate and severe. However, due to variation in data it is important to integrate the mean value over 14 days of hospital visit into a machine learning model to predict patient severity.

The study indicated that the measurements for moderate and severe patients remained abnormal over a long period. Only for certain measurements and after 10th day of stay mean data started progressing toward normal values, hence can play a role in the prediction of severe COVID cases. The systolic blood pressure, body temperature, oxygen saturation, MCHC, and MDRD GFR are suitable predictors for differentiating between moderate and severe after 10 days of stay in the hospital. The information after 10th day could be more useful in differentiating severe cases from the moderate case.

This longitudinal study is useful in understanding temporal variations in measurements, collected during the hospital stay and their importance in predicting the severity of patients. The course of hospital stay can be divided into two parts: less than 10 days and 10 to 14 days. And the information within these time frames can be integrated with the machine learning model to differentiate the mild patients in the early course of hospital stay, and the severe patients after the 10th day. These models can be important clinical decision support tools, and the expected trajectories for many vital signs and laboratory values among patients with different clinical severities can contribute to clinician decision-making about what a patient will need.

References

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Supplementary Figures

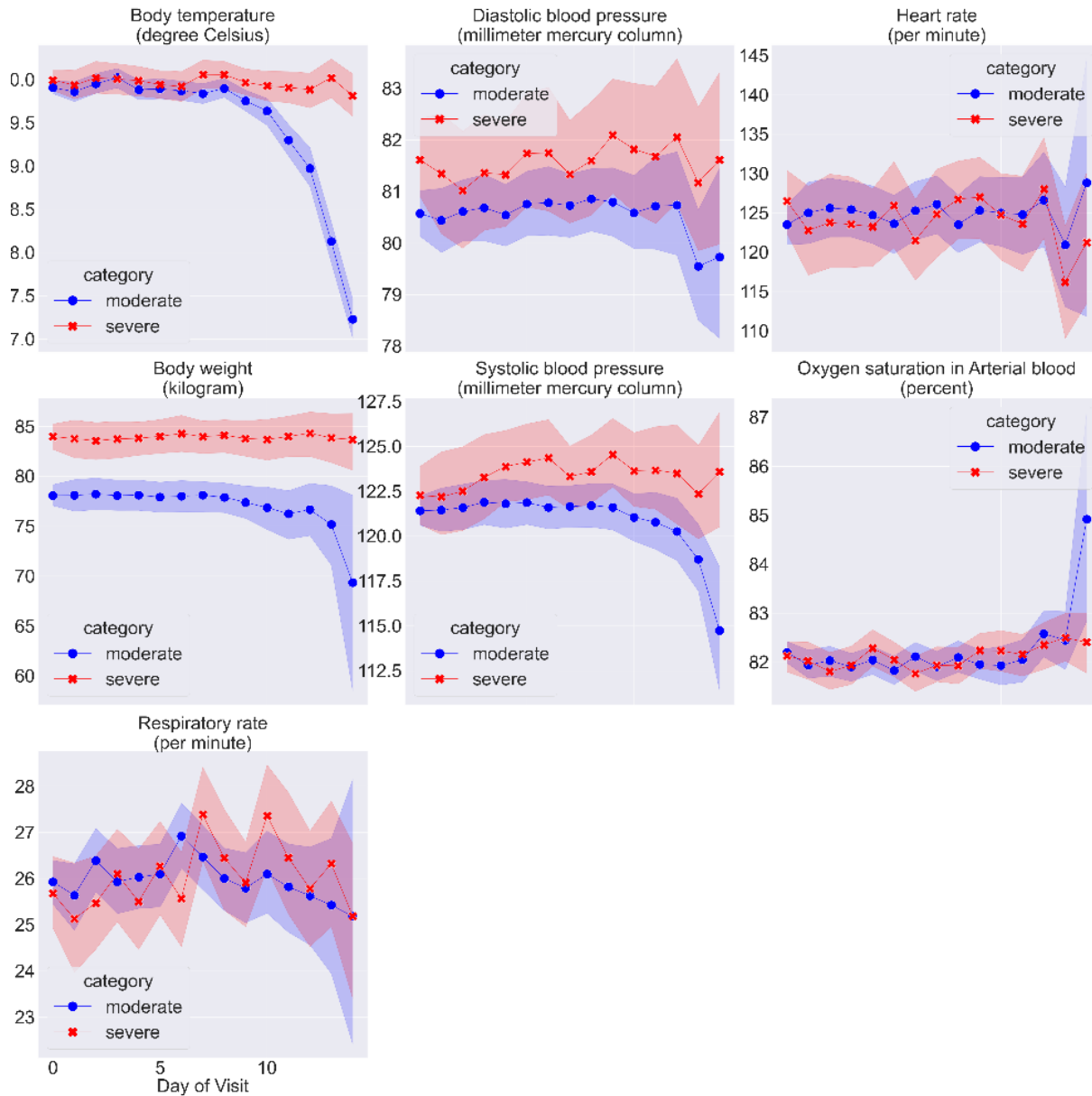


Figure S1 The mean (line) and interquartile range (shaded region) of each vital sign on each hospital day for moderate [blue], and severe [red] COVID-19.

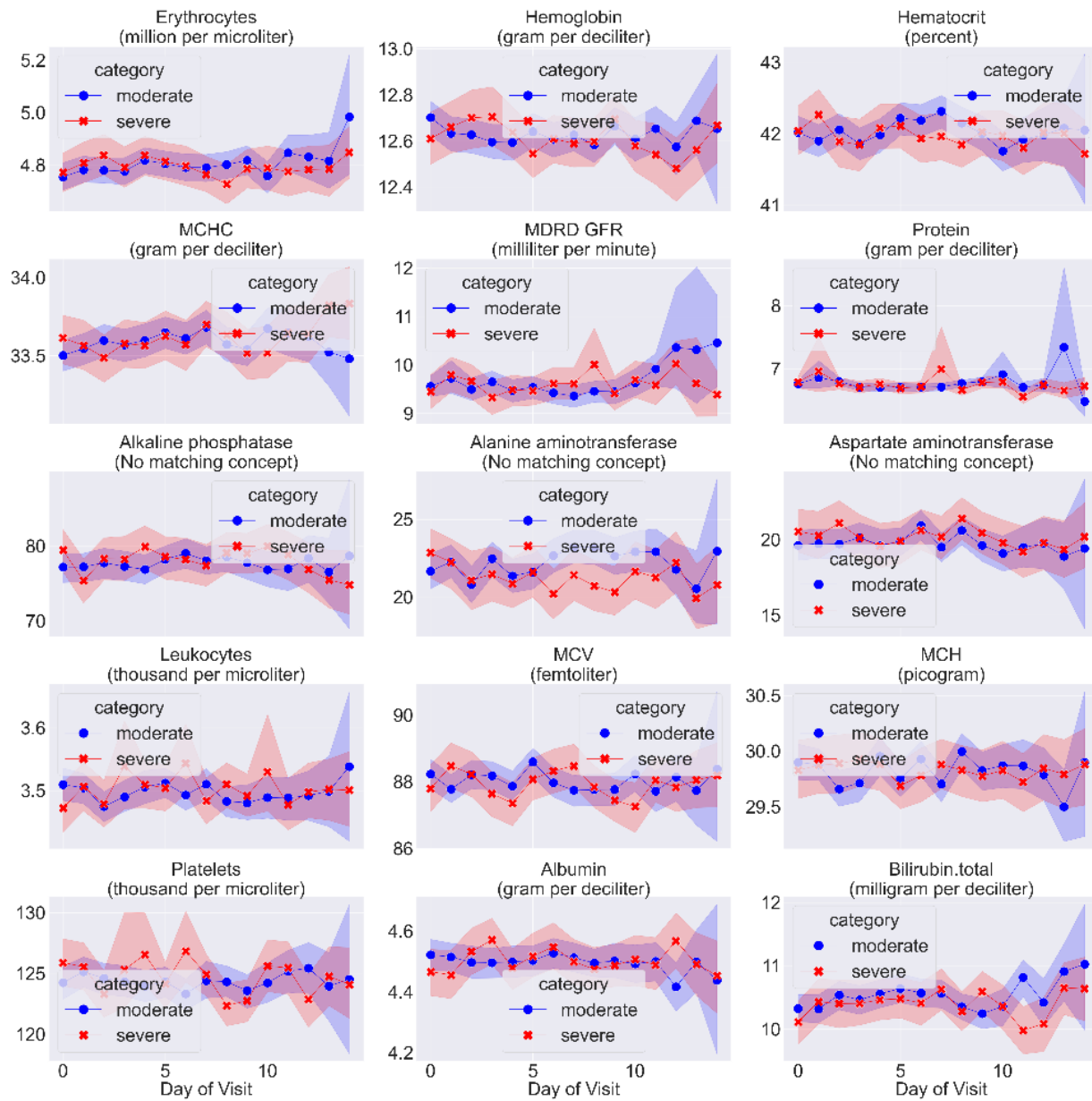


Figure S2 The mean (line) and interquartile range (shaded region) of each laboratory measurements on each hospital day for moderate [blue], and severe [red] COVID-19.